Clinical trial results:
A RANDOMIZED DOUBLE BLIND PLACEBO CONTROLLED PARALLEL GROUP STUDY OF THE EFFICACY AND SAFETY OF PREGABALIN (BID) IN SUBJECTS WITH POST TRAUMATIC PERIPHERAL NEUROPATHIC PAIN.

Summary

EudraCT number	2012-003304-12
Trial protocol	DE DK BG HU BE HR
Global end of trial date	04 August 2015

Results information

Result version number	v1 (current)
This version publication date	05 August 2016
First version publication date	05 August 2016

Trial information

Trial identification

Sponsor protocol code	A0081279

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01701362
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer Clinical Trials.gov Call Center, Pfizer, Inc, 001 18007181021 x, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer Clinical Trials.gov Call Center, Pfizer, Inc, 001 18007181021 x, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 August 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 August 2015
Global end of trial reached?	Yes
Global end of trial date	04 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of pregabalin (150-600 mg/day) compared with placebo in the treatment of chronic post-traumatic peripheral neuropathic pain.

Protection of trial subjects:

The study was conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).
In addition, the study was conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 43
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Poland: 41
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	South Africa: 5
Country: Number of subjects enrolled	Sweden: 27
Country: Number of subjects enrolled	United States: 362
Worldwide total number of subjects	539
EEA total number of subjects	163

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	437
From 65 to 84 years	101
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 187 centers participated in the study in 14 countries.

Pre-assignment

Screening details:

Single-blind screening period. Criteria such as chronic neuropathic pain for >6 months post trauma/surgeries as per medical history and not due to other causes like post herpetic neuralgia, trigeminal neuralgia; meeting other criteria for neuropathic pain assessment; and diagnosis of certain psychiatric conditions were considered.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Pregabalin

Arm description:

Participants randomized to receive pregabalin: a 3-week dose optimization phase followed by 150 mg, 300 mg, 450 mg or 600 mg per day dosing 12-week maintenance phase.

Arm type	Experimental
Investigational medicinal product name	Pregabalin
Investigational medicinal product code	
Other name	Lyrica
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

orally BID, with or without food

Arm title	Placebo

Arm description:

Participants randomized to receive placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

orally BID, with or without food

Number of subjects in period 1	Pregabalin	Placebo
Started	274	265
Completed	233	211
Not completed	41	54
Adverse events related to study drug	12	10
Adverse event, serious fatal	-	1
Reasons other than those mentioned above	3	5
No longer willing to participate	8	14
Lost to follow-up	6	9
Adverse events not related to study drug	1	6
Protocol deviation	5	3
Insufficient clinical response	6	6

Baseline characteristics

Reporting groups	
Reporting group title	Pregabalin
Reporting group description:	
Participants randomized to receive pregabalin: a 3-week dose optimization phase followed by 150 mg, 300 mg, 450 mg or 600 mg per day dosing 12-week maintenance phase.	
Reporting group title	Placebo
Reporting group description:	
Participants randomized to receive placebo	

Reporting group values	Pregabalin	Placebo	Total
Number of subjects	274	265	539
Age, Customized			
Only participants enrolled in the study who received at least one dose of study drug have been included here.			
Units: Participants			
Age Continuous			
Units: Years			
arithmetic mean	52.8	53.4	
standard deviation	± 12.9	± 12.7	-
Gender, Male/Female			
Only number of participants who enrolled and received at least one dose of study drug have been included here.			
Units: Participants			
Female	132	134	266
Male	142	131	273

End points

End points reporting groups

Reporting group title	Pregabalin
Reporting group description:	
Participants randomized to receive pregabalin: a 3-week dose optimization phase followed by 150 mg, 300 mg, 450 mg or 600 mg per day dosing 12-week maintenance phase.	
Reporting group title	Placebo
Reporting group description:	
Participants randomized to receive placebo	

Primary: Baseline Mean Pain Score

End point title	Baseline Mean Pain Score[1]
End point description:	
This is based on the daily pain dairy and is defined as the baseline mean pain diary score. The Daily Pain Diary consists of an 11-point numeric rating scale (NRS) ranging from 0 (“no pain”) to 10 (“worst possible pain”). Subjects describe their pain during the past 24 hours by choosing the appropriate number between 0 and 10.	
End point type	Primary
End point timeframe:	
Baseline	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this primary endpoint

End point values	Pregabalin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	265		
Units: units on a scale				
arithmetic mean (standard deviation)	6.41 (± 1.3)	6.54 (± 1.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline to Week 15 in Weekly Mean Pain Score

End point title	Change from Baseline to Week 15 in Weekly Mean Pain Score
End point description:	
This is based on the daily pain diary and is defined as the change from baseline to week 15 in mean pain diary score. The Daily Pain Diary consists of an 11-point numeric rating scale (NRS) ranging from 0 (“no pain”) to 10 (“worst possible pain”). Subjects describe their pain during the past 24 hours by choosing the appropriate number between 0 and 10.	
End point type	Primary
End point timeframe:	
up to Week 15	

End point values	Pregabalin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	265		
Units: units on a scale				
least squares mean (standard error)	-2.12 (± 0.15)	-1.9 (± 0.16)		

Statistical analyses

Statistical analysis title	Primary endpoint
Statistical analysis description:	
Mixed Model Repeated Measures (MMRM) method used here includes fixed categorical effects of treatment, country, trauma type, visit week, treatment-by-visit interaction, and a fixed continuous effect of baseline value. Missing mean pain scores were imputed by multiple imputation method.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1823
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	least squares mean difference
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.16

Secondary: Patient Global Impression of Change (PGIC) at Week 15

End point title	Patient Global Impression of Change (PGIC) at Week 15
End point description:	
A self administered instrument that measures changes in participants' overall status on a scale ranging from 1 (very much improved) to 7 (very much worse). The PGIC is based on the Clinical Global Impression of Change, which is a validated scale.	
End point type	Secondary
End point timeframe:	
Week 15	

End point values	Pregabalin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	265		
Units: proportion of participants				
Very much improved	52	41		
Much improved	105	79		
Minimally improved	61	62		
No change	34	51		
Minimally worse	5	9		
Much worse	0	4		
Very much worse	1	0		
MIssing	0	3		

Statistical analyses

Statistical analysis title	PGIC at Week 15
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0012 [2]
Method	Cochran-Mantel-Haenszel

Notes:

[2] - The p-value is derived from CMH test, stratified for pooled center and trauma type and excludes missing values.

Secondary: Change from baseline in overall weekly mean sleep interference score (SIRS)

End point title	Change from baseline in overall weekly mean sleep interference score (SIRS)

End point description:

This is an 11-point NRS ranging from 0 (“pain does not interfere with sleep”) to 10 ("pain completely interferes with sleep" [unable to sleep due to pain]). Participants describe how pain has interfered with their sleep during the past 24 hours. Please note that the data for Baseline (raw scores) have been included in the below table to read the change from Baseline data in context.

End point type	Secondary

End point timeframe:

up to Week 15

End point values	Pregabalin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	265		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (raw scores) (N = 274, 265)	4.97 (± 2.3)	4.99 (± 2.27)		
Week 1 (N = 260, 258)	-0.66 (± 1.1)	-0.28 (± 0.91)		
Week 2 (N = 254, 244)	-1.15 (± 1.51)	-0.81 (± 1.27)		
Week 3 (N = 252, 245)	-1.55 (± 1.73)	-1.14 (± 1.45)		

Week 4 (N = 245, 229)	-1.73 (± 1.8)	-1.3 (± 1.63)		
Week 5 (N = 241, 226)	-1.87 (± 1.87)	-1.4 (± 1.68)		
Week 6 (N = 244, 227)	-1.94 (± 1.95)	-1.46 (± 1.79)		
Week 7 (N = 240, 216)	-2.01 (± 1.99)	-1.5 (± 1.78)		
Week 8 (N = 236, 212)	-2.05 (± 2)	-1.52 (± 1.76)		
Week 9 (N = 232, 214)	-2.09 (± 1.99)	-1.55 (± 1.86)		
Week 10 (N = 229, 212)	-2.04 (± 2.11)	-1.55 (± 1.83)		
Week 11 (N = 230, 211)	-2.09 (± 2.05)	-1.64 (± 1.79)		
Week 12 (N = 227, 209)	-2.17 (± 2.06)	-1.68 (± 1.89)		
Week 13 (N = 225, 204)	-2.19 (± 2.06)	-1.7 (± 1.9)		
Week 14 (N = 222, 208)	-2.19 (± 2.16)	-1.79 (± 1.89)		
Week 15 (N = 196, 186)	-2.13 (± 2.17)	-1.83 (± 1.87)		
Overall (N = 269, 262)	-1.83 (± 1.93)	-1.37 (± 1.71)		

Statistical analyses

Statistical analysis title	Week 1
Statistical analysis description:	
Analyzed for treatment, center, trauma type, week & treatment-by-week interaction and fixed continuous effect of baseline value on the ITT population.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0119
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	least square mean difference
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	-0.08
Variability estimate	Standard error of the mean
Dispersion value	0.14

Statistical analysis title	Week 2
Statistical analysis description:	
Analyzed for treatment, center, trauma type, week & treatment-by-week interaction and fixed continuous effect of baseline value on the ITT population.	
Comparison groups	Pregabalin v Placebo

Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0135
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	least square mean difference
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	-0.07
Variability estimate	Standard error of the mean
Dispersion value	0.14

Statistical analysis title	Week 3

Statistical analysis description:

Analyzed for treatment, center, trauma type, week & treatment-by-week interaction and fixed continuous effect of baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0028
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	least square mean difference
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	-0.14
Variability estimate	Standard error of the mean
Dispersion value	0.14

Statistical analysis title	Week 4

Statistical analysis description:

Analyzed for treatment, center, trauma type, week & treatment-by-week interaction and fixed continuous effect of baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo

Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0016
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	least square mean difference
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	-0.17
Variability estimate	Standard error of the mean
Dispersion value	0.14

Statistical analysis title	Week 5

Statistical analysis description:

Analyzed for treatment, center, trauma type, week & treatment-by-week interaction and fixed continuous effect of baseline value on the ITT
population.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0007
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	least square mean difference
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.14

Statistical analysis title	Week 6

Statistical analysis description:

Analyzed for treatment, center, trauma type, week & treatment-by-week interaction and fixed continuous effect of baseline value on the ITT
population.

Comparison groups	Pregabalin v Placebo

Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0006
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	least square mean difference
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	-0.21
Variability estimate	Standard error of the mean
Dispersion value	0.14

Statistical analysis title	Week 7

Statistical analysis description:

Analyzed for treatment, center, trauma type, week & treatment-by-week interaction and fixed continuous effect of baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0008
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	least square mean difference
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.14

Statistical analysis title	Week 8

Statistical analysis description:

Analyzed for treatment, center, trauma type, week & treatment-by-week interaction and fixed continuous effect of baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo

Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0003
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	least square mean difference
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.79
upper limit	-0.24
Variability estimate	Standard error of the mean
Dispersion value	0.14

Statistical analysis title	Week 9

Statistical analysis description:

Analyzed for treatment, center, trauma type, week & treatment-by-week interaction and fixed continuous effect of baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0001
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	least square mean difference
Point estimate	-0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	-0.26
Variability estimate	Standard error of the mean
Dispersion value	0.14

Statistical analysis title	Week 10

Statistical analysis description:

Analyzed for treatment, center, trauma type, week & treatment-by-week interaction and fixed continuous effect of baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo

Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0005
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	least square mean difference
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	-0.22
Variability estimate	Standard error of the mean
Dispersion value	0.14

Statistical analysis title	Week 11

Statistical analysis description:

Analyzed for treatment, center, trauma type, week & treatment-by-week interaction and fixed continuous effect of baseline value on the ITT
population.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0007
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	least square mean difference
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.14

Statistical analysis title	Week 12

Statistical analysis description:

Analyzed for treatment, center, trauma type, week & treatment-by-week interaction and fixed continuous effect of baseline value on the ITT
population.

Comparison groups	Pregabalin v Placebo

Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0001
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	least square mean difference
Point estimate	-0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	-0.27
Variability estimate	Standard error of the mean
Dispersion value	0.14

Statistical analysis title	Week 13

Statistical analysis description:

Analyzed for treatment, center, trauma type, week & treatment-by-week interaction and fixed continuous effect of baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	least square mean difference
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.84
upper limit	-0.28
Variability estimate	Standard error of the mean
Dispersion value	0.14

Statistical analysis title	Week 14

Statistical analysis description:

Analyzed for treatment, center, trauma type, week & treatment-by-week interaction and fixed continuous effect of baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo

Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0005
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	least square mean difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	-0.22
Variability estimate	Standard error of the mean
Dispersion value	0.14

Statistical analysis title	Week 15

Statistical analysis description:

Analyzed for treatment, center, trauma type, week & treatment-by-week interaction and fixed continuous effect of baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0031
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	least square mean difference
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.71
upper limit	-0.14
Variability estimate	Standard error of the mean
Dispersion value	0.15

Statistical analysis title	Overall

Statistical analysis description:

Analyzed for treatment, center, trauma type, week & treatment-by-week interaction and fixed continuous effect of baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo

Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0001
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	least square mean difference
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.71
upper limit	-0.23
Variability estimate	Standard error of the mean
Dispersion value	0.12

Secondary: Change from baseline in Pain Severity Index (Brief Pain Inventory-short form [BPI-sf])

End point title	Change from baseline in Pain Severity Index (Brief Pain Inventory-short form [BPI-sf])

End point description:

A self-administered questionnaire developed to assess the severity of pain and the impact of pain on daily functions during the 24 hour period prior to evaluation. The BPI-sf consists of 5 questions. Four items measure pain on 11-point response scales from 0 to 10 ("No Pain" to "Pain as bad as you can imagine").

End point type	Secondary

End point timeframe:

Week 15

End point values	Pregabalin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	265		
Units: units on a scale				
least squares mean (standard error)	-2.4 (± 0.13)	-1.95 (± 0.13)		

Statistical analyses

Statistical analysis title	pain severity index: change from Baseline

Statistical analysis description:

This secondary endpoint has been analyzed using ANCOVA with model terms of treatment, center, trauma type and baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo

Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.005
Method	ANCOVA
Parameter estimate	least squares mean difference
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	-0.14
Variability estimate	Standard error of the mean
Dispersion value	0.16

Secondary: Change from baseline in Pain Interference Index (BPI-sf)

End point title	Change from baseline in Pain Interference Index (BPI-sf)

End point description:

The BPI-sf is a self-administered questionnaire developed to assess the severity of pain and he impact of pain on daily functions. Another item of the pain scale, containing 7 sub-questions, evaluates the level of pain interference with daily functioning on 11-point response scales from 0 to 10 (“Does not interfere” to “Completely interferes").

End point type	Secondary

End point timeframe:

Week 15

End point values	Pregabalin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	265		
Units: units on a scale				
least squares mean (standard error)	-1.72 (± 0.13)	-1.33 (± 0.13)		

Statistical analyses

Statistical analysis title	pain interference index: change from baseline

Statistical analysis description:

This secondary endpoint has been analyzed using ANCOVA with model terms of treatment, center, trauma type and baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo

Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0168
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.07
Variability estimate	Standard error of the mean
Dispersion value	0.16

Secondary: Change from baseline to endpoint in quality of life using EuroQol (EQ-5D) health state profile scores

End point title	Change from baseline to endpoint in quality of life using EuroQol (EQ-5D) health state profile scores

End point description:

A self-administered questionnaire designed to assess health related quality of life in terms of a single index value or utility score. There are 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 3 point response scale and the scores are combined to form a single index value between 0 and 1 with higher scores being more positive (better health status).

End point type	Secondary

End point timeframe:

Week 15

End point values	Pregabalin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	265		
Units: units on a scale				
least squares mean (standard error)				
Mobility	-0.1 (± 0.03)	-0.09 (± 0.03)		
Self-care	-0.08 (± 0.02)	-0.06 (± 0.02)		
Usual activities	-0.12 (± 0.03)	-0.13 (± 0.04)		
Pain/Discomfort	-0.35 (± 0.03)	-0.29 (± 0.04)		
Anxiety/Depression	0.01 (± 0.03)	-0.02 (± 0.03)		
Dolan 1997 Index Score	0.12 (± 0.01)	0.11 (± 0.01)		
Dolan 2001 Index Score	-0.13 (± 0.02)	-0.12 (± 0.02)		

Statistical analyses

Statistical analysis title	Mobility

Statistical analysis description:

This secondary endpoint has been analyzed using ANCOVA with model terms of treatment, center, trauma type and baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6841
Method	ANCOVA
Parameter estimate	least squares mean difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.06
Variability estimate	Standard error of the mean
Dispersion value	0.037

Statistical analysis title	Self-care

Statistical analysis description:

This secondary endpoint has been analyzed using ANCOVA with model terms of treatment, center, trauma type and baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6564
Method	ANCOVA
Parameter estimate	least squares mean difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.029

Statistical analysis title	Usual activities

Statistical analysis description:

This secondary endpoint has been analyzed using ANCOVA with model terms of treatment, center, trauma type and baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo

Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.859
Method	ANCOVA
Parameter estimate	least squares mean difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.043

Statistical analysis title	Pain/Discomfort

Statistical analysis description:

This secondary endpoint has been analyzed using ANCOVA with model terms of treatment, center, trauma type and baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1628
Method	ANCOVA
Parameter estimate	least squares mean difference
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.043

Statistical analysis title	Anxiety/Depression

Statistical analysis description:

This secondary endpoint has been analyzed using ANCOVA with model terms of treatment, center, trauma type and baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4654
Method	ANCOVA
Parameter estimate	leaset squares mean difference
Point estimate	0.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.037

Statistical analysis title	Dolan 1997 Index score

Statistical analysis description:

This secondary endpoint has been analyzed using ANCOVA with model terms of treatment, center, trauma type and baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5
Method	ANCOVA
Parameter estimate	least squares mean difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.017

Statistical analysis title	Dolan 2001 Index Score

Statistical analysis description:

This secondary endpoint has been analyzed using ANCOVA with model terms of treatment, center, trauma type and baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5493
Method	ANCOVA
Parameter estimate	leaset squares mean difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.026

Secondary: Mean baseline scores in the Medical Outcomes Study Sleep Scale (MOS-SS) - Sub-domain Score.

End point title	Mean baseline scores in the Medical Outcomes Study Sleep Scale (MOS-SS) - Sub-domain Score.

End point description:

The Baseline scores for the self-administered measure consisting of twelve items that assess the key constructs of sleep. Subjects are asked to recall sleep-related activities over the past week. Instrument scoring results in 7 subscales: sleep disturbance, snoring, awaken short of breath or with headache, quantity of sleep, optimal sleep, sleep adequacy, somnolence.

End point type	Secondary

End point timeframe:

Baseline

End point values	Pregabalin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	265		
Units: units on a scale				
arithmetic mean (standard deviation)				
Sleep Disturbance Score (N = 274, 265)	46.04 (± 25.791)	45.33 (± 25.08)		
Sleep Adequancy Score (N = 274, 265)	46.57 (± 28.153)	44.23 (± 28.582)		
Snoring Score (N = 272, 263)	33.09 (± 33.482)	35.89 (± 34.084)		
Awaken Short of Breath Score (N = 274, 265)	16.79 (± 25.647)	13.89 (± 21.541)		
Quantity of Sleep Score (hours) (N = 273, 265)	6.09 (± 1.36)	6.16 (± 1.411)		
Somnolence Score (N = 274, 265)	29.44 (± 21.618)	28.18 (± 19.884)		
Sleep Problem Index (9) Score (N = 274, 265)	41.11 (± 20.282)	40.64 (± 19.72)		
Optimal Sleep Score (N = 273, 265)	0.34 (± 0.476)	0.38 (± 0.487)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in the Medical Outcomes Study Sleep Scale (MOS-SS) - Sub-domain Score.

End point title	Mean change from baseline in the Medical Outcomes Study Sleep Scale (MOS-SS) - Sub-domain Score.

End point description:

A self-administered measure consisting of twelve items that assess the key constructs of sleep.Subjects are asked to recall sleep-related activities over the past week. Instrument scoring results in 7 subscales: sleep disturbance, snoring, awaken short of breath or with headache, quantity of sleep, optimal sleep, sleep adequacy, somnolence.

End point type	Secondary
End point timeframe:	
Week 15	

End point values	Pregabalin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	265		
Units: Number				
least squares mean (confidence interval 95%)				
Sleep Disturbance Score (N = 257, 245)	-14.71 (-17.57 to -11.85)	-11.24 (-14.16 to -8.33)		
Sleep Adequancy Score (N=257, 245)	10.13 (6.49 to 13.76)	8.16 (4.43 to 11.89)		
Snoring Score (N = 257, 245)	-2.22 (-5.46 to 1.03)	-3.27 (-6.59 to 0.04)		
Awaken Short of Breath Score (N = 257, 245)	-3.61 (-6.3 to -0.92)	-3.03 (-5.78 to -0.27)		
Quantity of Sleep Score (hours) (N = 257, 245)	0.42 (0.19 to 0.66)	0.26 (0.03 to 0.5)		
Somnolence Score (N = 257, 245)	-1.61 (-3.99 to 0.77)	-3.74 (-6.17 to -1.31)		
Sleep Problem Index (9) Score (N = 257, 245)	-9.86 (-12.17 to -7.56)	-8.19 (-10.55 to -5.83)		
Optimal Sleep Score (N = 256, 245)	0.11 (0.05 to 0.18)	0.04 (-0.03 to 0.1)		

Statistical analyses

Statistical analysis title	Sleep Disturbance Score
Statistical analysis description:	
This secondary endpoint has been analyzed using ANCOVA with model terms of treatment, center, trauma type and baseline value on the ITT population.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0545
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	7
Variability estimate	Standard error of the mean
Dispersion value	1.8

Statistical analysis title	Sleep Adequancy Score

Statistical analysis description:

This secondary endpoint has been analyzed using ANCOVA with model terms of treatment, center, trauma type and baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3913
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.47
upper limit	2.54
Variability estimate	Standard error of the mean
Dispersion value	2.29

Statistical analysis title	Snoring Score

Statistical analysis description:

This secondary endpoint has been analyzed using ANCOVA with model terms of treatment, center, trauma type and baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6059
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.06
upper limit	2.96
Variability estimate	Standard error of the mean
Dispersion value	2.04

Statistical analysis title	Awaken Short of Breath Score

Statistical analysis description:

This secondary endpoint has been analyzed using ANCOVA with model terms of treatment, center, trauma type and baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7317
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.76
upper limit	3.93
Variability estimate	Standard error of the mean
Dispersion value	1.7

Statistical analysis title	Quantity of Sleep Score (hours)

Statistical analysis description:

This secondary endpoint has been analyzed using ANCOVA with model terms of treatment, center, trauma type and baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2663
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	0.12
Variability estimate	Standard error of the mean
Dispersion value	0.15

Statistical analysis title	Somnolence Score

Statistical analysis description:

This secondary endpoint has been analyzed using ANCOVA with model terms of treatment, center, trauma type and baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo

Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1562
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.08
upper limit	0.82
Variability estimate	Standard error of the mean
Dispersion value	1.5

Statistical analysis title	Sleep Problem Index (9) Score

Statistical analysis description:

This secondary endpoint has been analyzed using ANCOVA with model terms of treatment, center, trauma type and baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.249
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.18
upper limit	4.53
Variability estimate	Standard error of the mean
Dispersion value	1.45

Statistical analysis title	Optimal Sleep Score

Statistical analysis description:

This secondary endpoint has been analyzed using ANCOVA with model terms of treatment, center, trauma type and baseline value on the ITT population.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0609
Method	ANCOVA
Parameter estimate	leaet squares mean difference
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.04

Secondary: Percentage of participants in MOS-SS with optimal sleep status.

End point title	Percentage of participants in MOS-SS with optimal sleep status.

End point description:

MOS-SS optimal sleep status analyzed on a scale of four parameters: any improvements, no change, any worsening and not applicable.

End point type	Secondary

End point timeframe:

Week 15

End point values	Pregabalin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	265		
Units: Percentage of participants				
number (not applicable)				
Any Improvements	21.2	18.5		
No Change	66.1	60.8		
Any Worsening	6.2	13.2		
Not applicable	6.6	7.5		

Statistical analyses

Statistical analysis title	Optimal sleep status
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7165 [3]
Method	Cochran-Mantel-Haenszel

Notes:

[3] - p-values based on CMH test stratified by pooled center and trauma type, patients with unknown status at baseline or endpoint will not be included in thecalculation of p-values.

Secondary: Percentage of responders to treatment with pregabalin measured as reduction in mean pain score of ≥30%.

End point title	Percentage of responders to treatment with pregabalin measured as reduction in mean pain score of ≥30%.

End point description:

Participants with at least 30% reduction in the mean pain score from baseline to each week. Weekly mean pain NRS scores are derived from the daily pain NRS and calculated as the mean of the available scores in the 7 days. Generally, week 'n' mean pain score is defined as the mean of the 7 daily diary pain ratings from Day 2+7*(n-1) to Day 1+7*n. At least 4 entries within the last 7 days are required to calculate a mean score. Scores range from 0 (no pain) to 10 (worst possible pain), with higher scored indicating increased pain.

End point type	Secondary

End point timeframe:

Week 15

End point values	Pregabalin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	265		
Units: Percentage of participants				
number (not applicable)				
Week 1 (N = 260, 258)	11.92	5.04		
Week 2 (N = 254, 244)	27.17	20.08		
Week 3 (N = 252, 245)	38.89	30.2		
Week 4 (N = 246, 229)	41.87	34.5		
Week 5 (N = 241, 226)	45.64	38.05		
Week 6 (N = 244, 227)	48.77	41.41		
Week 7 (N = 240, 216)	49.58	43.06		
Week 8 (N = 236, 213)	50.42	46.48		
Week 9 (N = 232, 214)	50.86	47.66		
Week 10 (N = 229, 212)	52.84	47.17		
Week 11 (N = 231, 211)	52.38	51.18		
Week 12 (N = 227, 209)	54.63	52.63		
Week 13 (N = 226, 204)	57.08	54.41		
Week 14 (N = 223, 208)	57.4	54.33		
Week 15 (N = 196, 187)	57.65	58.29		

Statistical analyses

Statistical analysis title	Week 1

Statistical analysis description:

Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0028
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	3.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	6.86

Statistical analysis title	Week 3
Statistical analysis description:	
Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0235
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	2.45

Statistical analysis title	Week 2
Statistical analysis description:	
Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.036
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	2.68

Statistical analysis title	Week 4

Statistical analysis description:	
Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0619
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	2.24

Statistical analysis title	Week 5
Statistical analysis description:	
Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0677
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	2.2

Statistical analysis title	Week 6
Statistical analysis description:	
Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0707
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.45

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	2.16

Statistical analysis title	Week 7
Statistical analysis description:	
Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1313
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	2.06

Statistical analysis title	Week 8
Statistical analysis description:	
Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3072
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.86

Statistical analysis title	Week 9

Statistical analysis description:

Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3947
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.8

Statistical analysis title	Week 11

Statistical analysis description:

Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6854
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.64

Statistical analysis title	Week 10

Statistical analysis description:

Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1462
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	2.05

Statistical analysis title	Week 12
Statistical analysis description:	
Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5025
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.74

Statistical analysis title	Week 13
Statistical analysis description:	
Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4908
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.76

Statistical analysis title	Week 14

Statistical analysis description:

Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4245
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.8

Statistical analysis title	Week 15

Statistical analysis description:

Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8464
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.49

Secondary: Percentage of responders to treatment with pregabalin measured as reduction in mean pain score of ≥50%

End point title	Percentage of responders to treatment with pregabalin measured as reduction in mean pain score of ≥50%

End point description:

Participants with at least 50% reduction in the mean pain score from baseline to each week. Weekly mean pain NRS scores are derived from the daily pain NRS and calculated as the mean of the available scores in the 7 days. Generally, week 'n' mean pain score is defined as the mean of the 7 daily diary pain ratings from Day 2+7*(n-1) to Day 1+7*n. At least 4 entries within the last 7 days are required to calculate a mean score. Scores range from 0 (no pain) to 10 (worst possible pain), with higher scored indicating increased pain.

End point type	Secondary

End point timeframe:

Week 15

End point values	Pregabalin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	265		
Units: Percentage of participants				
number (not applicable)				
Week 1 (N = 260, 258)	4.62	2.33		
Week 2 (N = 254, 244)	11.42	6.97		
Week 3 (N = 252, 245)	22.62	13.47		
Week 4 (N = 246, 229)	25.2	17.9		
Week 5 (N = 241, 226)	28.22	19.47		
Week 6 (N = 244, 227)	29.51	22.91		
Week 7 (N= 240, 216)	30.42	22.22		
Week 8 (N = 236, 213)	33.05	27.7		
Week 9 (N = 232, 214)	34.05	26.17		
Week 10 (N = 229, 212)	32.75	26.42		
Week 11 (N = 231, 211)	34.2	25.59		
Week 12 (N = 227, 209)	37.89	26.79		
Week 13 (N = 226, 204)	35.84	27.45		
Week 14 (N = 223, 208)	37.67	29.81		
Week 15 (N = 196, 187)	39.8	34.22		

Statistical analyses

Statistical analysis title	Week 1
Statistical analysis description:	
Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1633
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	2.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	6

Statistical analysis title	Week 2

Statistical analysis description:

Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0652
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	3.85

Statistical analysis title	Week 3

Statistical analysis description:

Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0039
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.29
upper limit	3.77

Statistical analysis title	Week 4

Statistical analysis description:

Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0382
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.71

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	2.83

Statistical analysis title	Week 5
Statistical analysis description:	
Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0137
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.14
upper limit	3.05

Statistical analysis title	Week 6
Statistical analysis description:	
Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0693
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	2.49

Statistical analysis title	Week 7

Statistical analysis description:

Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0349
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	2.73

Statistical analysis title	Week 8

Statistical analysis description:

Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1227
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	2.29

Statistical analysis title	Week 9

Statistical analysis description:

Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0364
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.65

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	2.63

Statistical analysis title	Week 10
Statistical analysis description:	
Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0667
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	2.49

Statistical analysis title	Week 11
Statistical analysis description:	
Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0176
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	2.84

Statistical analysis title	Week 12

Statistical analysis description:

Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.003
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	2.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.27
upper limit	3.23

Statistical analysis title	Week 13

Statistical analysis description:

Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0256
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	2.74

Statistical analysis title	Week 14

Statistical analysis description:

Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0314
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.66

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	2.64

Statistical analysis title	Week 15

Statistical analysis description:

Model terms include categorical: treatment, center, trauma type, week, and treatment-by-week interaction; and continuous: baselines mean pain score.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1889
Method	Gen linear model-logistic link function
Parameter estimate	Odds ratio (OR)
Point estimate	1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	2.21

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The active reporting period was from the signing of the informed consent throughout the study including 28 calendar days from the last dose of study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Pregabalin

Reporting group description:

Participants randomized to receive pregabalin: a 3-week dose optimization phase followed by 150 mg, 300 mg, 450 mg or 600 mg per day dosing 12-week maintenance phase.

Reporting group title	Placebo

Reporting group description:

Participants randomized to receive placebo

Serious adverse events	Pregabalin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 274 (0.73%)	7 / 265 (2.64%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 274 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 274 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Post procedural discharge			
subjects affected / exposed	0 / 274 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	1 / 274 (0.36%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 274 (0.36%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic seizure			
subjects affected / exposed	1 / 274 (0.36%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haemorrhoids			
subjects affected / exposed	0 / 274 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 274 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 274 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Major depression			
subjects affected / exposed	0 / 274 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Lumbar spinal stenosis			
subjects affected / exposed	0 / 274 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 274 (0.36%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 274 (0.36%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Pregabalin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 274 (27.37%)	33 / 265 (12.45%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	40 / 274 (14.60%)	11 / 265 (4.15%)	
occurrences (all)	51	13	
Somnolence			
subjects affected / exposed	27 / 274 (9.85%)	9 / 265 (3.40%)	
occurrences (all)	31	10	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	14 / 274 (5.11%)	10 / 265 (3.77%)	
occurrences (all)	16	10	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	14 / 274 (5.11%)	8 / 265 (3.02%)	
occurrences (all)	15	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2014	1.) Change in sample size to a maximum of 700 subjects. Enrollment to continue beyond n=470 until interim analysis results are available. Rationale: to permit enrolling additional subjects if recommended by the study Data Monitoring Committee based on the results of the interim analysis. 2.) Change analysis method for primary efficacy variable to Mixed Model Repeated Measures (MMRM) from Analysis of Covariance (ANCOVA). ANCOVA will become a sensitivity analysis. Rationale: to make more efficient use of weekly mean pain scores. 3.) Change analysis method for sample size re-estimation to be performed by the Data Monitoring Committee at the interim analysis. Rationale: to allow for more efficient use of data in the final analysis. 4.) Change decision rules to be used by the Data Monitoring Committee to make a sample size re-estimation recommendation based on the results of the interim analysis. Rationale: to make more efficient use of data at the interim and final analyses. 5.) Language changed to facilitate subject access to appropriately qualified medical personnel on study related medical questions or problems, to clarify information regarding medication errors, adverse event reporting and communication of study results by Pfizer.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported